HERPES

Increase in rates of herpes simplex virus type 1 as a cause of anogenital herpes in western Sydney, Australia, between 1979 and 2003

L J Haddow, B Dave, A Mindel, K A McPhie, C Chung, C Marks, D E Dwyer

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Correspondence to: Professor Adrian Mindel, Sexually Transmitted Infections Research Centre, Westmead Hospital, Westmead, New South Wales 2145, Australia; adrianm@icpmr.wsahs.nsw.gov.au

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Backgound/objective: Recent studies suggest that herpes simplex virus type 1 (HSV-1) is becoming more common as a cause for genital herpes, relative to HSV-2. We aimed to calculate trends in HSV type from isolates and serology samples sent to a reference virology laboratory in New South Wales (NSW), Australia.

Methods: We compared the proportions of HSV-1 and HSV-2 positive samples, adjusting for age and sex of source patient, in three datasets: anogenital isolates from 1979 to 1988; anogenital isolates from 1989 to 2003; and HSV type specific IgM seropositivity from 1994 to 2003.

Results: The number of specimens in each analysis was 17 512, 4359, and 497, respectively. There was a progressive rise in the proportions of typed specimens being HSV-1 in all analyses. The proportion of isolates that were HSV-1 ranged from 3% in 1980 to 41% in 2001. Female sex and age under 25 were associated with a greater proportion of HSV-1 isolates in both time periods. In the period 1979–88, comparing the proportions of HSV-1 and HSV-2 gave an odds ratio (OR) per additional year of 1.24 (95% confidence interval (CI) 1.20 to 1.27; $p<0.005$) after adjustment for age and sex. In the period 1989–2003 there was a steeper rise in the proportion of isolates that were HSV-1 in samples from younger individuals (OR per year 1.17, 1.12 to 1.22) compared to those over 25 (OR per year 1.06, 1.03 to 1.08). The rise in the proportion of IgM seropositive results reactive for HSV-1 compared to HSV-2 gave an OR of 1.36 per year (1.26 to 1.47; $p<0.005$).

Conclusions: These data suggest that HSV-1 has become more common as a cause of anogenital herpes in NSW.

Anogenital infection with herpes simplex viruses types 1 and 2 (HSV-1 and HSV-2) is one of the commonest sexually transmitted diseases in the world,[1 2] and is responsible for serious physical and psychological consequences.[3] There are few studies of trends of relative proportions of types 1 and 2 infection in Australia,[4] but evidence from the United States and Europe suggests that HSV-1 is increasingly associated with genital infection.[5–10] These trends may result from lower rates of pre-pubertal HSV-1, changing sexual practices with regard to orogenital sexual contact, and earlier age of first sexual intercourse. They have important implications for overall rates in symptomatic genital herpes, incidence of herpes acquisition, rates of neonatal herpes infection, and provision of a protective vaccine.[11]

The aim of this study was to measure changes in the proportion of anogenital isolates and HSV type specific IgM serology that were HSV-1 positive in New South Wales (NSW), Australia since 1979.

METHODS

The study included all anogenital HSV isolates in patients aged over 10 years from 1979 to 2003 that were obtained by the Department of Virology, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital. Specimens came from patients attending a number of general practice centres, sexual health clinics, and hospitals in NSW. From 1989 onwards, general practitioners had greater access to privately managed diagnostic HSV testing, therefore the specimens were mainly sourced from sexual health clinics and overall numbers decreased. Another fall in specimen numbers occurred in 2002 when molecular based HSV testing became available for clinical use at other sites. Requests for HSV type specific IgM at the same site between 1994 and 2003 were also included.

Swabs, tissue, vesicle fluid, and other specimens intended for HSV culture were received by the laboratory in virus transport medium. Only samples from anal and genital body sites (including adjacent areas such as buttock, pubic area, and upper thigh) were included in the study. Samples were inoculated onto MRC-5 human diploid fibroblasts and incubated for 7 days. Daily observation for cytopathic effects identified isolates, which were then typed using an immunofluorescent antibody test (IFAT) with HSV-1 and HSV-2 monoclonal antibodies (Syva MicroTrak HSV-1/HSV-2, Behring Diagnostics Inc, Cupertino, CA, USA). An older polyclonal antibody system was used in the early 1980s, although this would not have produced significantly different typing results.

Blood samples were tested for the presence of HSV-1 and HSV-2 IgM using a western blot method developed in our laboratory.[14] Weak positive results were considered to be positive and equivocal results negative.

Positive HSV type specific IgM results and isolates were subject to further analysis. Duplicate identities, where any patient had more than one positive isolate, were excluded by deleting the later record. De-identified data were obtained from laboratory records and details of virus isolation and serology were tabulated in a database by year. Age and sex data were also available for source patients for anogenital HSV isolates (but not serology). Data for isolates in 1994 were

Abbreviations: HSV, herpes simplex virus; ICPMR, Institute of Clinical Pathology and Medical Research; IFAT, immunofluorescent antibody test

Table 1 Summary statistics for anogenital isolates studied, including age and sex of source and immunofluorescent antibody test type (IFAT)

	Early period 1979–1988		Late period 1989–2003		Total	
	No	%	No	%	No	%
Number of specimens	17 512		4359		21 871	
IFAT type						
1	1713	9.8	1014	23.3	2727	12.5
2	13 792	78.8	3343	76.7	17 135	78.3
Not typed	2001	11.4	2	<0.1	2003	9.2
Sex						
Male	8130	46.4	1910	43.8	10 040	45.9
Female	8461	48.3	2351	54.0	10 812	49.4
Not recorded	921	5.3	98	2.2	1019	3.7
Age						
Over 25	6370	36.4	2932	67.3	9302	42.5
25 and under	4074	23.3	815	18.7	4889	22.4
Not recorded	7068	40.4	612	14.0	7680	35.1

missing because of a computer system upgrade. Owing to the change in source of specimens in 1989, the data were analysed in two periods, 1979–88 and 1989–2003.

Statistical analysis was performed using SPSS software. Simple cross tabulation was performed to determine numbers of HSV-1 isolates as a proportion of the total isolates each year. Curve estimation was used to determine whether quadratic or linear terms best fitted the model, and interactions between all three parameters were assessed. Associations between proportions of HSV-1 and year, age, and sex were calculated as odds ratios (OR) using logistic regression. The earlier records were known to lack age data in many cases, but missing data were not specifically controlled for, except by normal logistic regression methods.

Ethical approval was obtained from the local human research ethics committee.

RESULTS

Anogenital isolates

Between 1979 and 2003, a total of 21 871 HSV-1 or HSV-2 anogenital isolates were collected from patients aged 10 and above. During the same time period, 4201 isolates were obtained from other body sites, 8598 isolates from unknown body sites, and 119 anogenital isolates were obtained from children under 10.

A breakdown of all HSV anogenital isolates is given in table 1. Age was frequently unrecorded in the early period (1979–88). The proportion of missing age data varied between years but there was no apparent trend to this feature of the dataset, and adjustment was made for age in the later multivariate analysis. Of those patients in whom age was recorded, 4074 out of 10 444 (39%) were 25 and under in the early period, compared to 815 of 3747 (22%) in the late period.

Figure 1 shows the number of typed isolates annually. A significant proportion (11.4%) of anogenital swabs were not typed in the early period. This was because of a temporary discontinuation of routine typing of genital isolates in 1985 and 1986, when 1735 out of 4291 isolates (40.4%) were not typed.

Figure 2 shows the proportion of specimens that were type 1 each year, including typed HSV anogenital isolates and IgM type specific antibodies. Type specific IgM was detected in 497 sera collected between 1994 and 2003. Of these, 205 (41%) were HSV-1 IgM seropositive only, 283 (57%) were HSV-2 IgM seropositive only, and nine (2%) were seropositive for HSV-1 and HSV-2 IgM .

The figure demonstrates a rise over time in the proportion of IgM results that were HSV-1 reactive. Comparing the proportions between consecutive years gives an OR of 1.36

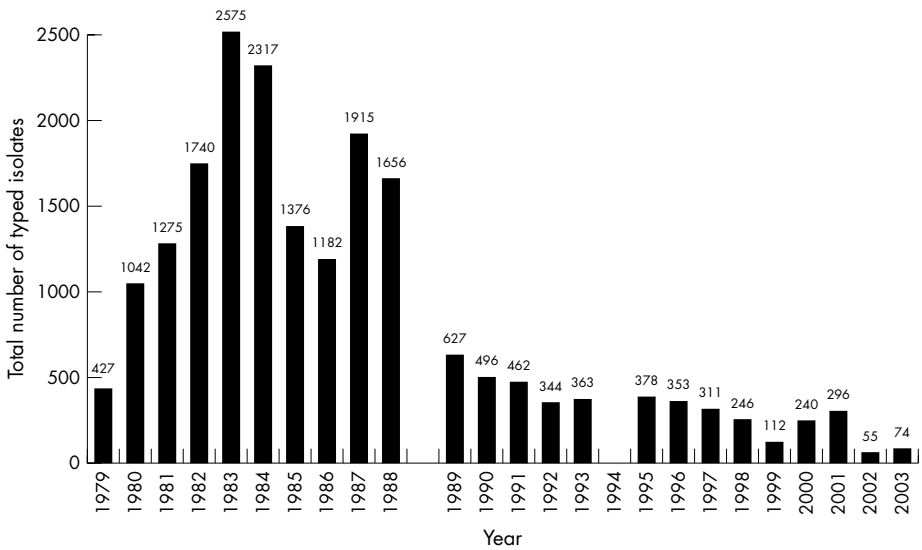

Figure 1 Annual numbers of typed isolates processed by the laboratory. Changes in numbers of isolates typed are discussed in the methods and results.

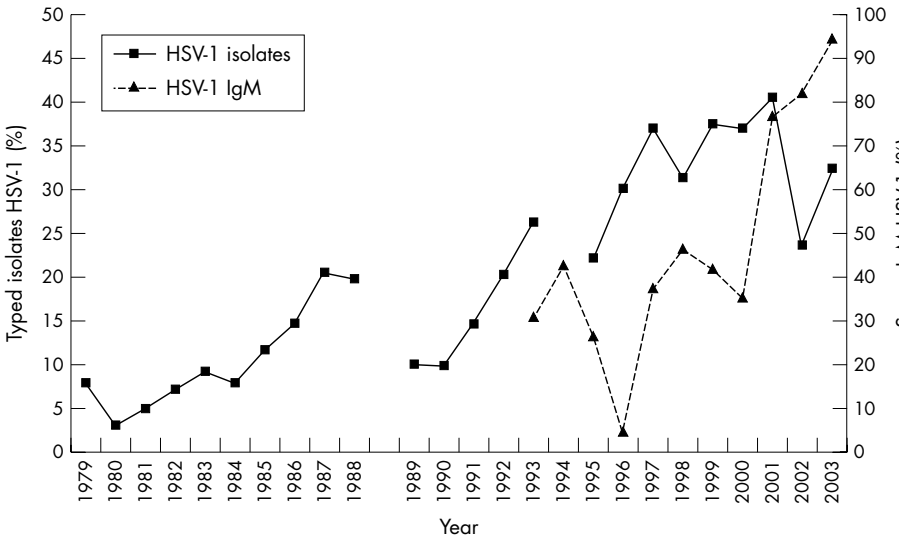

Figure 2 The solid line shows percentage of typed HSV isolates from anogenital samples that were type 1 in two time periods from 1979 to 1988 (n = 15 511) and 1989 to 2003 (n = 4357). The minimum proportion of isolates that were HSV-1 was 3% (in 1980) and the maximum was 41% (in 2001). The broken line shows the proportion of positive type specific IgM ELISA results that showed HSV-1 reactivity (n = 497).

(1.26 to 1.47; $p<0.005$) for each additional year. These results are similar to the trends found in anogenital isolates.

Effect of age and sex

Univariate analysis (table 2) to compare annual proportion of anogenital isolates that were type 1 between males and females and between patients over 25 and under 26 found that females had higher odds of having HSV-1 (and not HSV-2) than males and younger patients had higher rates than older. These effects were seen in both time periods and there was a clear upward trend in all patient groups. Comparing the OR per additional year for males and females in each time period and age group found no difference between the sexes for the rate of increase in likelihood of type 1 being isolated (data not shown).

Multivariate analysis is also summarised in table 2. In the early period of analysis (1979–88), after adjustment for all variables the likelihood of an isolate being type 1 from a patient aged 25 years and under was greater than in those from older patients. Similarly, samples from females were more likely to be HSV-1 than from males. Tests for interaction between parameters showed that there was no association between age and sex in either time period. In the later period (1989–2003) there was a steeper rise in rates of HSV-1 isolation in samples from younger individuals compared to those over 25 ($p<0.005$). In 3 years out of the last 6 years, over 60% of isolates from younger patients were HSV-1.

DISCUSSION

This study provides laboratory evidence for increasing proportions of anogenital herpes caused by HSV-1 in NSW (chiefly western Sydney and environs), Australia, between 1979 and 2003. Younger patients and women had higher rates of HSV-1 as a cause of anogenital herpes throughout the study period. The trend is more marked in younger patients, after 1989. As both HSV types were common, care must be taken not to interpret the figures presented as risks and thus overestimate the rate of the increase.

The findings are consistent with previous studies in other developed countries.[5 7–10] In contrast with other Australian

Table 2 Results of logistic regression analysis showing proportion of anogenital HSV cultures being type 1 according to year of sample, age, and sex

		Univariate analysis		Multivariate analysis	
Time period	**Variable**	**OR**	**95% CI***	**OR**	**95% CI***
Early 1979–88 (n = 9143)	Year of sample	1.25	1.22 to 1.28	1.24	1.20 to 1.27
	Age				
	Over 25	1		1	
	25 and under	1.97	1.75 to 2.23	1.71	1.51 to 1.95
	Sex				
	Male	1		1	
	Female	2.93	2.61 to 3.28	2.50	2.16 to 2.90
Late 1989–2003	**Age over 25 (n = 2896):**				
	Year of sample	1.07	1.05 to 1.10	1.06	1.03 to 1.08
	Sex				
	Male	1		1	
	Female	2.91	2.37 to 3.59	2.76	2.24 to 3.41
	Age 25 and under (n = 797):				
	Year of sample	1.19	1.14 to 1.24	1.17	1.12 to 1.22
	Sex				
	Male	1		1	
	Female	2.66	1.89 to 3.74	2.24	1.57 to 3.20

Figures for year of sample represent change in odds of being type 1 and not type 2, per additional year. The number of records analysed differs from n given in table 1 because of missing data, mainly patient age. Variables were analysed as linear terms, the best fit model for these data. OR = odds ratio, CI = confidence interval. *p Value <0.001 in all cases.

data[4] we did not find any evidence of males ''catching up'' with females in HSV-1 rates, there being no difference between the sexes' rate of rise. This study also differs from previous studies in that both serological specimens and viral isolates were used, from a similar population and time period. The data are particularly valuable as they include a very large number of subjects over more than 20 years of data collection.

This study lacks clinical, behavioural, and demographic data, so it was not possible to undertake analysis according to contact with same sex partners or a history of recent orogenital intercourse, for example. NSW contains large minority populations of Aboriginal Australians, people of east Asian ethnicity, and those of lower socioeconomic status, who may exhibit different trends in HSV incidence. Our database does not record whether the specimen was taken during a primary, initial, or recurrent episode, and the recurrence rate of HSV-1 is lower than HSV-2,[12] so more patients with symptomatic HSV-2 may have been identified. It is also notable that in the first decade of the analysis a large number of age data were missing, and we accept this as a shortcoming in this historical analysis.

We only recorded HSV isolates from samples received by our laboratory. It is assumed that standard medical practice in Australia includes diagnostic testing in instances of suspected herpes, but many factors may influence the decision to send a sample to our facility. The analysis was divided into early and late time periods to reduce one source of bias: a shift towards other diagnostic services. The likelihood of a sample yielding an isolate is variably dependent on the age of the lesion and the technique of the sampler, regardless of laboratory standardisation and quality control. For these reasons the study cannot fully reflect the incidence and prevalence of symptomatic HSV-1 and HSV-2 in the community.

Previous work in our local sexual health clinic showed that older adults, particularly heterosexual men, are more likely to receive herpes antibody testing.[13] Approximately 20% of recurrences produce positive HSV IgM on ELISA testing; the clinical value of IgM testing is discussed in the literature.[14 15]

Neonatal herpes infection carries a mortality rate of 29% in disseminated disease after higher dose aciclovir and had a mortality of 85% in the pre-antiviral era,[16] as well as long term sequelae in survivors. Australian surveillance data show an incidence of 3.38 per 100 000 live births,[17] lower than that seen in the United States, which may reflect different patterns of epidemiology.[18] Unlike the United States, HSV-1 is the predominant isolate causing neonatal infection in Australia, and an increase in HSV-1 anogenital disease may translate to an increase in neonatal HSV-1 infection such as that observed in Netherlands.[19]

A vaccine to prevent HSV-2 infection has shown efficacy in women who are HSV-1 seronegative.[11 20] Epidemiological studies are useful to inform the timing and provision of such a vaccine. In a recent survey of Australian adolescents, 56.7% of students in the final year of secondary education reported having given or received oral sex in the previous year, often without having had sexual intercourse.[21] Although the prevalence of HSV-1 is around 75% in Australian adults over 25,[22] rates in pre-adolescent children are thought to be low and surveys are ongoing to determine the age at which most people become infected with HSV-1. In parts of the developed world, HSV-1 may now be considered a prominent STI among young people, and health promotion interventions and ''safe sex'' messages aimed at this group need to be tailored accordingly.

Key messages

- The proportion of anogenital HSV isolated by western Sydney's virology reference laboratory that were type 1 rose between 1979 and 2003, from less than 10% in the early 1980s to around 35% in the late 1990s and early 2000s
- Younger age and female sex are associated with a greater proportion of anogenital HSV isolates being type 1
- The proportion of HSV isolates found to be type 1 has risen more steeply in specimens from patients aged 25 years and under since 1989
- The findings in this suburban sample are similar to other studies from developed nations

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This study's main findings were presented in abstract form at the Australasian Sexual Health Conference in Hobart, Tasmania, August 2005.

CONTRIBUTORS

LH and BD contributed equally to the project and manuscript; BD performed initial data collection, analysis and presentation; LH performed further analysis and was responsible for later drafts of the manuscript; the initial concept was devised by BD, DD, and AM; database management was also performed by KM, CC, and CM; KM and DD were responsible for laboratory methods; all authors commented on the final manuscript, particularly AM and DD; submission to the journal and response to reviewers was done by LH.

Authors' affiliations

L J Haddow, A Mindel, C Chung, C Marks, Sexually Transmitted Infections Research Centre, University of Sydney and Centre for Infectious Diseases and Microbiology, Westmead Hospital, Westmead, New South Wales 2145, Australia

B Dave, K A McPhie, D E Dwyer, Centre for Infectious Diseases and Microbiology Laboratory Services, Institute for Clinical Pathology and Medical Research, Westmead Hospital, Westmead, New South Wales 2145, Australia

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